IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Chopp | Confirmation No.: 2465

Serial No. 10/500,694 | Group Art Unit: 1609

Filed: 12/21/04 | Examiner: WEBB, Walter E.

For: NITRIC OXIDE DONORS FOR TREATMENT OF DISEASE AND INJURY

Attorney Docket No: 1059.00106

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION

I, Dr. Michael Chopp, being duly sworn, do hereby state that:

1. I am the inventor of the above-captioned application.

2. I am skilled in the art and have worked extensively in the field of neurology and specifically with ischemic stroke.

3. Claims 1-2 and 8-13 stand rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for administering sildenafil or hMSC to ischemic rats, does not reasonably provide enablement for promoting neurogenesis in an ischemic patient in general by administering a phosphodiesterase type 5 inhibitor and cellular therapy. The Office Action holds that undue experimentation would be required to practice the invention.

As I have previously presented in a Declaration, animal studies, and preclinical studies, form the basis for all drug research and development and the statements of the Office Action, likely, run counter to a myriad of patents. Many treatments and drugs have been developed and first tested in the animal and subsequently moved to the human. This is an FDA requirement. This is a standard process that one skilled in the art recognizes. The mechanism of action shown in the rat studies is also present in human studies. Neurogenesis is present in the human after stroke (*PNAS August 29, 2006 vol. 103 no. 35 13198-13202 -among others)* and it was first demonstrated in rodent (A Arvidsson, et al. - Nature Medicine, 2002 - among many others). The mechanisms of action of sildenafil, a phosphodiesterase

V inhibitor in the present invention, are the same as in the human. There is no reason to question the rat models of the present invention. They are directly predictive of results in humans, and one skilled in the art could practice the invention based on the studies shown in the specification.

Bjorklund, et al. is cited to show that cellular therapy in regard to treating ischemic stroke is not well settled in studies with rats. Bjorklund, et al. editorializes about the difficulty performing exogenously administered stem cell replacement studies in the rodent. Bjorklund, et al. states "without better knowledge of the biological mechanisms of improvement, and optimization of the functional outcome in animal models, cell therapy for patients with ischemic damage is unlikely to develop to a point of therapeutic value." There are a number of issues with this statement: 1) This is someone's OPINION, published 9 years ago, with no basis in fact; 2) The authors are not stroke experts, 3) They are discussing "cell replacement" therapies and not cell or pharmacological therapies that stimulate production of the brain's stem cells; and 4) Their statements are factually incorrect- there are excellent models of functional outcomes in animals, there have been major insights into mechanisms promoting improvement, and my laboratory as well as others have published extensively in this area. Thus, one skilled in the art would not regard the statements of Bjorklund, et al. as having relevance to the subject matter of the present invention.

The Office Action holds that the claims are very broad insofar as they suggest that neurogenesis can be promoted by administering phosphodiesterase type 5 inhibitors and cellular therapy in general. I note that the group of phosphodiesterase type 5 inhibitors encompasses a well-defined group, and one skilled in the art would expect one PDE5 inhibitor would function in the same manner as another. The claims have been amended to define cellular therapy as mesenchymal stem cells, without prejudice. While many types of cellular therapy would function in the same manner as mesenchymal stem cells, the examples of the present invention are directed to mesenchymal stem cells, and therefore there is direct support for this type of cellular therapy in combination with a PDE5 inhibitor in the specification.

The Office Action holds that more guidance is required to treat humans with the method disclosed, and cites Johansson to show that regeneration of transectioned central axons have never been convincingly demonstrated in higher mammals and that recovery from stroke seen in humans is likely due to

reorganization of cortical networks, and that recovery after stroke is time sensitive. Therefore, the Office Action holds that it is doubted that neurogenesis can be promoted in humans by simply administering a PDE 5 inhibitor and cellular therapy.

These comments of Johansson, as noted above for Bjorklund, are not data, but opinions provided in a recorded lecture. These comments do not in anyway preclude Applicant's ability to stimulate recovery of function using cells of drugs (e.g. PDE5 inhibitors). Transected axons are irrelevant to stroke. I and others have shown that axons can be stimulated to grow in the central nervous system (J Cereb Blood Flow Metab. 2008 Aug;28(8):1440-8. Epub 2008 Apr 16, *Stroke.* 2008;39:2571;The Journal of Neuroscience, July 7, 2004, 24(27):6209-6217; among others). The statement that recovery is likely the result of retraining brain, does not in anyway preclude Applicant's ability to stimulate and enhance this recovery. The comment by the Office Action that recovery from stroke is time sensitive, does not in anyway preclude treatment to enhance recovery. Nor do I propose that treatment is time independent. I have shown that the treatments of the present invention (MSCs, PDE5 inhibitor) provide functional benefit even when therapy is initiated one month post stroke. I do not claim that these treatments will be effective when initiated at all times, e.g. 5 years post stroke. The Office Action also holds "given that central axons have never been convincingly demonstrated and that recovery is time sensitive, it is doubted that neurogenesis can be promoted in humans by simply administering a PDE5 inhibitor and cellular therapy." The logic of this statement is irrational. It is a non-sequitor. In addition, the statement counters the best available scientific evidence that cellular and certain drug therapy promote neurogenesis in the laboratory. There is no basis as noted above to preclude this from occurring in the human, and all evidence suggests that neurogenesis occurs in the human and the biology of the human and the animal are similar. If one would follow the "logic" of the Office Action, there would be no science.

Since the specification is fully supportive for promoting neurogenesis in an ischemic patient by administering a phosphodiesterase type 5 inhibitor and cellular therapy of mesenchymal stem cells, reconsideration of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

The undersigned declares further all statements made herein of his knowledge are true and that all statements made upon information and belief are believed to be true, and further that the statements were made with the knowledge that willful and false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 1/3, 2009

Dr. Michael Chapp